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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/931,951	08/20/2001	Nobuhiro Sato	213126US0X	4655

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/931,951	SATO ET AL.	
	Examin r	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 15-18* is/are pending in the application.

4a) Of the above claim(s) *1-13 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

FINAL ACTION

1. This Office Action is responsive to Applicant's amendment and response filed October 28, 2002. Claim 14 had been cancelled. Claims 16-18 have been added.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

Objection/Rejections Withdrawn

3. In view of Applicant's amendment the following Objections and Rejections have been withdrawn:

a)Objection to the specification, page 2, paragraph 2 of previous Office action.
b) Rejection of claim 14 under 35 U.S.C. 102(b), pages 9-10, paragraph 5 of the previous Office action.

Rejection Maintained

4. The rejection under 35 U.S.C. 112, second paragraph is maintained for newly presented claims 16-18 for the reasons set forth on page 8, paragraph 4 of the previous Office Action.

The rejection was on the grounds that the claims rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: 1) providing a sample (i.e. sample source, 2) determining that the target antibody (i.e. *Fusobacterium varium*) is obtained and not antibodies to a mixture of colonic bacteria, 3) determining the amount of antibody significant to make a diagnosis and 4) the correlation as to how to a diagnose of ulcerative colitis is made using the antibody.

Applicant urges that the 35. U.S.C. 112, second paragraph rejection is obviated by the amendment. Applicant urges that claim 14 has been cancelled and rewritten as claims 16-18 to insert method steps.

Applicant's arguments filed October 28, 2002 have been fully considered but they are not persuasive. The claims are incomplete for omitting essential steps. For example, how was the patient sera obtained? How were the ELISA and Western blotting methods used, were whole *Fusobacterium varium* organisms used to detect antibodies or were proteins of *F. varium* (antigens) used in the assays? What controls were used in the ELISA? What controls were used in the Western blot? It is the Examiner's position that claims 16-18 are indefinite and do not meet the requirement of 35 U.S.C. 112, second paragraph.

5. The rejection under 35 U.S.C. 112, first paragraph is maintained for newly presented claims 16-18 for the reasons set forth pages 6-8, paragraph 8 of the previous Office Action.

The rejection was on the grounds that the claim is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

16-18 Claim ~~14~~ is drawn to a method of diagnosis of ulcerative colitis.

The specification is only enabled for a method of detecting *Fusobacterium varium* antibodies and not a method of diagnosis of ulcerative colitis.

There are several factors that contribute to the diagnosis of a disease or disorder that are well known in the art. These factors include: 1) the known etiologic agent that causes the disease, 2) the cross reactivity of multiple microorganisms involved in the disease and 3) the immunopathogenesis associated with the disease. The etiologic agent associated with ulcerative colitis is unknown. This is evidenced by Sartor *(Gasreoenterology Clinic of North America (UNITED STATES), September 1995, 24, p. 475-507).* Sartor teaches that ulcerative colitis and Crohn's disease collectively are

referred to as inflammatory bowel disease (IBD), are chronic, spontaneously relapsing disorders of unknown cause (see the Abstract). Braegger *(Acta Paediatr Suppl. 395 : 18021, 1994)* teaches that the etiology and pathogenesis of chronic inflammatory bowel disease are unknown (see the Abstract). Fox et al *(Infection and Immunity, April 1999, p. 1757-1762)* suggest that *Helicobacter* species are associated with colitis (the Abstract). It is unpredictable as to which microorganisms may be involved in ulcerative colitis. This is evidenced by Macpherson et al *(Gut, 1996,38:365-375).* Macpherson et al suggest that there may be multiple organisms involved in inflammatory bowel disease. Macpherson et al disclose experiments that show that in relapse of inflammatory bowel disease there is a breakdown of tolerance to the normal commensal flora of the gut (which includes multiple organisms). Multiple microorganisms that reside in the gastrointestinal tract are evidenced by Coleman et al, *(Applied and Environmental Microbiology, October 1996, p. 3632-3639).* Coleman et al teach that there are six microbial competitors in the human gastrointestinal tract and they are *Escherichia coli, Enterobacter aergenes*, *Bacteroides ovatus, Fusobacterium varium* and *Enterococcus faecalis*. Cross-reactivity is a factor to be considered since there are multiple microorganisms that reside in the gastrointestinal tract. Marx et al *(Infection and Immunity, June 1982, 36 (3) p. 943-948)* teach that cross-reactivity exist between species of the genera *Bacteroides* and species of the genera *Fusobacterium* (see the Abstract). Ushijima et al *(Journal of Medical Microbiology, September 1990, 33 (10:17-22)* further teach that cross-reactivity exists between species of colonic bacteria (see the Abstract). Immunopathogenesis is also associated with ulcerative colitis. Braegger *(Acta Paediatr Suppl. 395 : 18021, 1994)* teaches that immunological mechanisms may play a significant role in mediating the intestinal lesion and some of the systemic manifestations of Crohn's disease and ulcerative colitis. Braegger teaches that Crohn's disease and ulcerative colitis present dense infiltration of inflammatory cells, increased plasma cells, T lymphocytes, macrophages and neutrophils (page 18, 1st column). Braegger further teaches that ulcerative colitis may be caused by an IgG-mediated autoimmune process to the colon mucosa (pages 20-21).

Since the detection of antibodies is used in the claimed invention to diagnose ulcerative colitis, one skilled in the art would have to possess the knowledge or be provided with sufficient guidance with regard as to how to detect only the target microorganism (i.e. *Fusobacterium varium*) and not a mixture of colonic bacteria antibodies in order to make a diagnosis of ulcerative colitis. The cited references have shown that unpredictability and uncertainty exists regarding which microorganism or microorganisms are the causative agents of ulcerative colitis. Other references have been cited that show that there are multiple microorganisms that reside in the gastrointestinal tract and references have also been cited to show the immunopathogenesis associated with the disease. Therefore, it can be concluded that undue experimentation would be required to use the claimed method of diagnosing ulcerative colitis without proper guidance.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention.

The specification fails to teach how a sample is obtained? How to determine the amount of antibody significant to make a diagnosis of ulcerative colitis? How to assure that the target antibody (i.e. *Fusobacterium varium*) is obtained and not a mixture of antibodies from other colonic bacteria? Nor does the specification provide a correlation between how to diagnosis of ulcerative colitis and the detection of *Fusobacterium varium* antibodies. Therefore, it is unclear as to how to make a diagnosis of ulcerative colitis using the claimed method.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification as to the etiologic agent that causes ulcerative colitis 3) there are limited working examples which suggest the detection of *Fusobacterium varium* antibodies 4) the relative skill of those in the art is commonly recognized as quite high (post - doctoral level), and the lack of predictability in the field to which the invention pertains is recognized in the art as evidenced by the cited prior art.

In view of all of the above, in view of the lack of predictability regarding the cross reactivity of microorganisms that inhabit the gastrointestinal tract and uncertainty of the etiologic agent of ulcerative colitis in the art, it is determined that it would require undue experimentation to use the claimed invention.

Applicant urges that those skilled in the art could easily carry out the method of claim 16 by using either a western blotting method or an enzyme-linked immunosorbent assay (ELISA). Applicant urges that Example 1 of the specification discloses that *Fusobacterium* can be isolated and an antibody specific thereto can be obtained. Therefore, the specification meets with the requirements prescribed by 35 U.S.C. 112.

Applicant's arguments filed October 28, 2002 have been fully considered but they are not persuasive. It is the Examiner's position that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make or use the invention. For example, the specification teaches that "in an ELISA and immunohistochemistry with *F. varium* proteins an (as) antigen, mean optical density and the detection rate were higher for our patients than for subjects with Crohn's disease or other controls" (page 8, Example 1). What were the controls used in the assays? What proteins of *F. varium* were used in the assays? How was mean optical density established? Did subjects with Crohn's disease or other diseases produce antibodies which could bind or be detected by F. *varium*? The specification does not provide any experimental data for the ELISA or immunohistochemistry testing mentioned in Example 1, therefore, how can it be concluded that the mean optical density and the detection rate for patients with ulcerative colitis be higher than subjects with Crohn's disease or other controls? It would appear from the information provided in Example 1, that subjects with Crohn's disease or diseases would also be detect in the ELISA and immunohistochemistry assays. Therefore, it can be concluded that the ELISA or immunohistochemistry tests use in Example 1 can be used to detect subjects with other disease such as Crohn's disease as well as subjects with ulcerative colitis. The specification has not provided a correlation between a method of making a diagnosis of ulcerative colitis in a patient and detecting *F. varium.* The specification states that " *F. varium* as commensal bacteria has not been recognized to be pathogenic, we found that colonic ulcers indued by enema of butyric acid which was produced by the bacterium" (page 3). The specification discloses that toxins produced by *F. varium* cells have toxicity to vero cells and the toxins were analyzed (page 4). The specification discloses that the principal component of the toxin produced by *F. varium*

was butyric acid (page 4). Can any other bacteria which produce butyric acid and have antibodies generated against it bind to *F. varium*?

While the use of ELISA and Western-blotting techniques are well known in the art, one skilled in the art would have to possess the knowledge or be provided with sufficient guidance as how to detect only the target microorganism (i.e. *Fusobacterium varium*) and not a mixture of colonic bacteria antibodies in order to make a diagnosis of ulcerative colitis since references (i.e. Sartor, 1995, Braeggar, 1994, Fox et al, 1999, Macpherson et al, 1996) cited in the previous Office action show that unpredictability and uncertainty exists regarding which microorganism or microorganisms are the causative agents of ulcerative colitis. Other references (i.e. Coleman et al, 1996, Marx et al, 1982 and Ushijima et al 1990) were cited to show that there are multiple microorganisms that reside in the gastrointestinal tract and were also cited to show the immunopathogenesis associated with the disease. The specification has failed to provide the guidance needed for the skilled artisan to use the claimed method in a manner that is commensurate with the claims. Therefore, it can be concluded that undue experimentation would be required to use the claimed method of diagnosing ulcerative colitis without proper guidance.

Status of Claims

6. No claims allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
January 8, 2003

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